Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures

U.S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Toxicology

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PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency (EPA) consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a research program for chemical mixtures that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development. These efforts are interrelated. For example, the trend testing suggests mixtures of concern for further research, the mixtures toxicological testing contributes to the design and calibration of the models and validation of the methodology, and the modeling and methodology efforts suggest further testing to resolve issues and enhance understanding.

In this manner, ATSDR scientists, in collaboration with mixtures risk assessors and laboratory scientists, have been evolving an approach to the assessment of the joint toxic action of chemical mixtures over a number of years. This body of work, including published articles and book chapters, government documents, meeting reports, and unpublished reports, is the foundation of this document.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS:

Sharon Wilbur, M.A.
Hugh Hansen, Ph.D.
Hana Pohl, M.C., Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Joan Colman, Ph.D.
William Stiteler, Ph.D., internal reviewer
Syracuse Research Corporation, North Syracuse, NY

THE GUIDANCE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEW:

Agency-wide review.

EXPERT PANEL REVIEW

An following expert panel was assembled to review this document on May 30-31, 2000.

Panel Members:

Vladimir Bencko, M.D., Ph.D.
Institute of Hygiene and Epidemiology
Charles University of Prague
Studnickova 7
CZ 128 00 Prague 2
Czech Republic

Ingvar Eide, Ph.D.
Statoil Research Centre
N-7005 Trondheim, Norway

Henry Gardner, Ph.D.
3407 Rolling Green Drive
Ft. Collins, CO 80525

Peter Grevatt, Ph.D.
U.S. Environmental Protection Agency
Office of Solid Waste & Emergency Response
Washington, DC

John Groten, Ph.D.
Department of Explanatory Toxicology
TNO Nutrition and Food Research Institute
Zeist, Netherlands

Richard Hertzberg, Ph.D.
Waste Management Division
U.S. Environmental Protection Agency
Atlanta, GA

Kannan Krishnan, Ph.D.
Human Toxicology Research Group
University of Montreal
Montreal, PQ, Canada

Scott Masten, Ph.D.
Environmental Toxicology Program
National Institute of Environmental
Health Sciences
Research Triangle Park, NC

Mark McClanahan, Ph.D.
Centers for Disease Control and Prevention
National Center for Environmental Health
Health Studies Branch
Atlanta, GA

Harihara Mehendale, Ph.D.
Department of Toxicology
College of Pharmacy
University of Louisiana
Monroe, LA

Joel Pounds, Ph.D.
Department of Molecular Biosciences
Pacific Northwest National Laboratory
Richland, WA

Jane Ellen Simmons, Ph.D.
U.S. Environmental Protection Agency
Research Triangle Park, NC

Madhusudan Soni, Ph.D.
Burdock and Associates, Inc.
Vero Beach, FL

Els van Vliet, Ph.D.
Health Council of the Netherlands
2500 BB Den Haag
The Netherlands

Raymond Yang, Ph.D.
Center for Environmental Toxicology
and Technology
Colorado State University
Fort Collins, CO

Technical Reviewer:

Patrick Durkin, Ph.D.
Syracuse Environmental Research Associates
Fayetteville, NY

These experts collectively have knowledge of experimental, statistical, and modeling methods for mixtures, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in this document. A listing of the reviewers' comments, with a brief explanation regarding their inclusion or the rationale for their exclusion, exists as part of the administrative record for this document.

The citation of the expert panel review should not be understood to imply its approval of the document's final content. The responsibility for the content of this document lies with the ATSDR.

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	Binary weight-of-evidence
BMD	benchmark dose
BTEXs	benzene, toluene, ethylbenzene and xylenes
CDD	chlorinated dibenzo-*p*-dioxin
CDF	chlorinated dibenzofuran
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
DNA	deoxyribonucleic acid
DT	Division of Toxicology
EMEG	environmental media evaluation guide
EPA	Environmental Protection Agency
FQPA	Food Quality Protection Act
HI	hazard index
HQ	hazard quotient
IRIS	Integrated Risk Information System
ISS	Integral Search System
kg	kilogram
LOAEL	lowest-observed-adverse-effect level
mg	milligram
MRL	Minimal Risk Level
NAS	National Academy of Science
NIEHS	National Institute for Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
OSHA	Occupational Safety and Health Administration
PAH	polycyclic aromatic hydrocarbon
PBPK/PD	physiologically based pharmacokinetic/pharmacodynamic
PCB	polychlorinated biphenyl
PEL	permissible exposure limit
ppm	parts per million
QSAR	quantitative structure-activity relationship
RfC	Reference Concentration
RfD	Reference Dose
SAR	structure-activity relationship
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalent
TLV	threshold limit value
TTD	target-organ toxicity dose
UF	uncertainty factor
U.S.	United States
WOE	weight-of-evidence

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to

EXECUTIVE SUMMARY

The *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures* (Mixtures Guidance Manual) is intended to assist environmental health scientists and toxicologists of ATSDR's Division of Toxicology (DT) in determining whether exposure to chemical mixtures at hazardous waste sites may impact public health. It serves a basis for interaction profiles, as the basis for health assessments and health consultations.

The ATSDR approach outlined in the Mixtures Guidance Manual is consistent with the approach articulated by EPA in 1986 and used to some extent, formally or informally, by a number of agencies. The approach is grounded in the law (CERCLA and the Food Quality Protection Act), and affords greater assurance of protection against adverse health effects than does the assessment of each chemical separately. The Expert Peer Review Panel, assembled on May 30-31, 2000 (see page iii), strongly approved of ATSDR's efforts to provide guidance for assessing joint toxic action of chemical mixtures and endorsed the ATSDR approach presented herein, which incorporates their comments and recommendations. The Mixture Guidance Manual also underwent ATSDR agency-wide review and incorporates comments received from these reviewers.

This guidance is designed to be used in conjunction with the ATSDR Public Health Assessment Guidance Manual, which provides the primary guidance for public health assessment, including aspects not covered in the Mixtures Guidance Manual. These additional aspects include exposure assessment guidance, recommended sources of health guideline values and toxicological information, and evaluation of health implications of other medical and toxicological factors, sensitive subpopulations, uncertainties, and community-specific health outcome data and community health concerns. The outcome of the public health assessment process is a determination of the category of public health hazard (ranging from urgent to no apparent public health hazard), and of follow-up actions including actions to protect public health, collection of additional health or site-characterization information, and community health education.

The systematic method outlined in the Mixtures Guidance Manual integrates ATSDR's interaction profiles, toxicological profiles, and research on chemical mixtures into a practical screening approach for potential health hazards. The conclusions from this exposure-based screening assessment of mixture hazard can then be taken into account *along with* biomedical judgment, the community-specific health outcome data, and community health concerns, to determine the public health implications and follow-up activities for a hazardous waste site.

The Mixtures Guidance Manual is organized so that the first three chapters provide background information considered important in understanding the ATSDR approach to mixtures assessment. The fourth chapter presents the ATSDR approach to exposure-based assessment of the joint toxic action of chemical mixtures. This approach is a semi-quantitative screening process. A step-by-step procedure is outlined in a flow chart for the assessment of noncarcinogenic effects and discussed in the accompanying text, followed by a series of examples illustrating the strategy. The strategy for the assessment of carcinogenic effects is then presented in a similar manner, with a flow chart, discussion, and series of examples.

The strategies for noncancer and cancer effects are similar. Exposure data and toxicological information on the mixture of concern (or a similar mixture) are the preferred basis for an assessment. If available, toxicological information on mixtures of concern for hazardous waste sites are likely to be reviewed and evaluated in ATSDR documents, including interaction profiles and toxicological profiles. If specific ATSDR documents or comparable documents from other agencies are not available, or do not provide Minimal Risk Levels (MRLs) or comparable health guideline values for the mixture or guidance regarding a health assessment approach, and if suitable whole mixture studies are not available, a components-based approach is undertaken.

The components-based approach focuses on mixture components that are present at toxicologically significant exposure levels, based on estimated exposures and relevant health guideline values. Linked physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for two or more components, if available, may be used to predict the potential for interactions, or possibly for noncancer or cancer health effects from the mixture. The hazard index method is used to screen for noncancer health hazards from potential additivity of the components. Cancer risks for the components are summed to screen for health hazards from potential additivity of carcinogenic effects. A weight-of-evidence method is used to evaluate the potential impact of interactions on noncancer and cancer health effects.

Additional technical detail regarding the concepts of dose and response addition, and the methodology for evaluating potential interactions, is provided in the appendices.